Exhibit A

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Suppression of Ischemia in Coronary Artery Disease (ACIP)

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Nitroglycerin Patches for Reducing Ischemia

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Heparin and Aspirin in Unstable Angina

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placebo or nitroglycerin patch therapy (0.4 mg/h), with a repeat exercise test a mean (±SD) of 6.1 ± 1.8 days later. Active patch therapy significantly reduced the total quantified perfusion defect size (−8.9 ± 11.1%) compared with placebo therapy (−1.8 ± 6.1%, p = 0.04), and this was most apparent in patients with the largest (≥20%) baseline perfusion defects (−11.4 ± 13.4% vs. 1.0 ± 3.6%, respectively, p < 0.02). Seven (33%) of 21 patients receiving active therapy had a ≥10% decrease in perfusion defect size compared with only 1 (5%) of 19 placebo-treated patients (p = 0.002). Short-term, intermittent nitroglycerin patch therapy significantly reduces myocardial ischemia as assessed by quantitative tomography.

(continued on page A-33)

JACC Vol. 24, No. 1
July 1994:39–45

Comparison of the Effect of Heparin and Aspirin Versus Aspirin Alone on Transient Myocardial Ischemia and In-Hospital Prognosis in Patients With Unstable Angina

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Objectives. This study compared the effects of heparin and aspirin versus aspirin alone on transient myocardial ischemia and in-hospital prognosis in patients with unstable angina.

Background. Transient myocardial ischemia occurring in patients with unstable angina is associated with an adverse prognosis. Heparin and aspirin are two drugs used frequently in the treatment of this condition, but the effect of combination therapy versus aspirin alone on transient myocardial ischemia is unknown.

Methods. Two hundred eighty-five consecutive patients with unstable angina were randomized to receive either intravenous heparin plus oral aspirin (150 mg once daily) (Group H + A) or aspirin alone (Group A). Patients also received a beta-adrenergic blocking agent, diltiazem and intravenous nitrates. ST segment monitoring was performed for the 1st 48 h of treatment. Patients were followed up for the duration of their in-hospital stay.

Results. One hundred fifty-four patients (30 women, mean [±SEM] age 58.3 ± 0.8 years) received heparin and aspirin (Group H + A), and 131 patients (26 women, mean age 60.6 ± 0.8 years) received aspirin only (Group A). ST segment monitoring (1,622 h) yielded 244 episodes of transient myocardial ischemia of a total duration of 7,819 min. There were no significant differences between the two treatment arms in the number of patients with transient myocardial ischemia (27 [18%] in Group H + A vs. 31 [24%] in Group A), number of episodes (96 in Group H + A vs. 148 in Group A) or total duration of transient myocardial ischemia (2,911 min in Group H + A vs. 4,908 min in Group A). The incidence of in-hospital myocardial infarction or death was significantly higher in patients with transient myocardial ischemia (53% vs. 22%, $p < 0.0001$). Five of the six deaths occurred in patients with transient myocardial ischemia. Event-free survival from myocardial infarction or death was similar in both treatment groups. Preadmission therapy with aspirin was associated with a lower in-hospital infarction rate (19% vs. 34%, $p = 0.01$).

Conclusions. The presence of transient myocardial ischemia in patients with unstable angina is associated with a significantly higher incidence of myocardial infarction or death in hospital. Combined therapy with heparin and aspirin compared with aspirin alone makes no difference in the development of these events, nor does it reduce the development of transient myocardial ischemia.

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The development of unstable angina is most commonly due to plaque rupture, with concomitant platelet activation and thrombus formation (1–3). Consequently, seemingly logical treatment strategies have evolved for the management of patients with unstable angina. There is compelling evidence from several large-scale trials that aspirin is beneficial in treating unstable angina (4–7). In contrast, placebo-controlled trials of heparin therapy have produced discordant results (6–8). Nonetheless, patients frequently receive both aspirin and heparin during the acute phase of unstable angina despite the lack of evidence from clinical trials that combination therapy is superior to treatment with aspirin alone.

The role of aspirin in the management of unstable angina is well established: thus, the real clinical question is not whether heparin is the same or better than aspirin, but whether combination therapy with heparin *and* aspirin confers any advantage to the patient over aspirin therapy alone. Because continuing myocardial ischemia identifies those patients with unstable angina who are at greater risk for subsequent cardiac events (9–11), we have addressed this issue by determining the effect of combination therapy with heparin and aspirin versus aspirin therapy alone on transient myocardial ischemia and in-hospital prognosis.

Methods

Consecutive patients with a clinical diagnosis of unstable angina who fulfilled the entry criteria entered a single-blind,

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randomized multicenter trial comparing the effects of heparin and aspirin versus aspirin alone on transient myocardial ischemia and in-hospital prognosis. Patients were recruited between October 1990 and October 1992 from three district general hospitals in the United Kingdom (Royal United Hospital, Bath; Hillingdon Hospital, Uxbridge; Wycombe General Hospital, High Wycombe). All data were analyzed centrally at the Royal Brompton National Heart and Lung Hospital.

A diagnosis of unstable angina was based on history of chest pain and included new onset of exertional chest pain <1 month in duration, the recent development of more readily provoked angina with episodes of increasing severity, duration and refractoriness to antianginal medication, rest or nocturnal chest pain thought to be due to myoeardial ischemia and angina occurring within 1 month after myocardial infarction (12). The most recent episode of chest pain had to have occurred within 24 h before randomization.

The inclusion criteria were a diagnosis of unstable angina, age 30 to 75 years inclusive and willingness to give written informed consent. The exclusion criteria were evidence of an evolving Q wave myocardial infarction on the admission electrocardiogram (ECG), clinical contraindications to heparin or aspirin administration, concomitant therapy with warfarin or other anticoagulants, thrombocytopenia (platelet count $<100 \times 10^{12}$/liter), pregnancy, diabetic proliferative retinopathy and ECG changes making interpretation of ST segment recordings impossible (complete left bundle branch block, left ventricular hypertrophy and changes associated with digoxin administration). The demonstration of reversible ST segment shift was not an entry criterion. Informed written consent was obtained from all patients entering the trial, in accordance with guidelines established by the ethical committees of all participating centers that approved the study.

Drug therapy. Patients were admitted to the coronary care unit and placed on strict bed rest for at least 48 h. Drug therapy was initiated immediately when the patient entered the trial. Unless contraindicated, patients received an intravenous infusion of nitrates for ≥48 h at the minimal dose required to render them pain free, oral beta-adrenergic blocking agents to maintain a rest heart rate <70 beats/min and diltiazem 60 mg orally three times a day. Beta-blocker and diltiazem therapy was continued throughout the hospital admission. Patients were randomized to receive either heparin and aspirin (150 mg orally once daily) (Group H + A) or aspirin alone (150 mg orally once daily) (Group A). Heparin was administered as an intravenous bolus of 5,000 U sodium heparin, followed immediately by a continuous infusion to maintain the activated partial thromboplastin time between 1.5 and 2.5 × baseline. The activated partial thromboplastin time was measured 4 to 6 h after initiating therapy and daily thereafter, and the dose of heparin was adjusted accordingly. The intended duration of heparin infusion was 48 h.

Additional blood tests. A full blood count and cardiac enzyme levels were measured on entry into the trial and daily thereafter for at least 48 h, or longer if the patient's condition had not stabilized.

Rest ECGs and ST segment monitoring. A resting 12-lead ECG was taken before entry into the study and daily thereafter until the patient's condition had stabilized. Additional recordings were made during episodes of typical chest pain. ST segment monitoring was performed in all patients during the 1st 48 h of treatment using a frequency-modulated dual-channel recorder (Oxford Medilog 2, frequency response 0.05 to 40 Hz). Tapes were applied by a trained member of the coronary care unit. Using pregelled electrodes, recordings were made from two bipolar leads (CM5 and a modified lead II). The sites and methods of application of the electrodes have been described elsewhere (13). A pain chart was kept for all patients during the period of ST segment monitoring to record the timing of episodes of chest pain.

Electrocardiographic and ST segment analysis. All ECGs were analyzed independently by one cardiologist. Abnormalities of rhythm, conduction disturbances, presence or development of pathologic Q waves and ST-T wave abnormalities were recorded. Where difficulties in interpretation arose, the opinion of a second cardiologist was sought. ST segment tapes were analyzed visually on an Oxford Medilog MA 20 analyzer at 60 to 120 times normal speed. Printouts were made at a paper speed of 25 mm/s. Significant ST segment depression was defined as planar or downsloping ST segment shift ≥1 mm measured 80 ms after the J point, compared with the rest recording of at least 60 s duration. Significant ST segment elevation was defined as ST elevation ≥2 mm measured at the J point of at least 60 s duration. An interval of at least 2 min was required after the resolution of one episode before another discrete episode was counted. Episodes of ST segment depression and elevation were also classified as either painful or silent, depending on the patient's symptoms recorded on the chest pain chart at that time. The results of ST segment monitoring were not disclosed to the attending physician.

Trial aims and definition of terms. The trial was designed to assess the effect of heparin and aspirin versus aspirin alone on transient myocardial ischemia and the development of myocardial infarction or death in hospital. Comparisons were made between the number of patients in each treatment group with episodes of transient myocardial ischemia, total number of episodes and total duration of ischemia. The incidence of death, myocardial infarction (fatal and nonfatal) and combined myocardial infarction or death in hospital were determined for both treatment groups, for patients with and without transient myocardial ischemia (irrespective of treatment) and for patients according to treatment and the presence or absence of transient myocardial ischemia. Myocardial infarction was defined as twofold or greater increase in cardiac enzyme levels in association with either severe chest pain of long duration or ECG changes characteristic of myocardial infarction (development of pathologic Q waves, loss of R wave amplitude, ST segment elevation with sub-

sequent T wave inversion). Electrocardiographic changes of posterior myocardial infarction were defined as anterior ST segment depression and R/S ratio >1 in leads V_1 or V_2. Non-Q wave infarction was defined as myocardial infarction without the development of significant Q waves. Secondary end points were referrals for cardiac catheterization because of the failure of medical therapy and revascularization by either coronary artery bypass surgery or coronary angioplasty.

Statistical analysis. The calculation of sample size was based on the expected incidence of transient myocardial ischemia and the effect of heparin alone and aspirin alone on transient myocardial ischemia (14). Assuming an incidence of transient myocardial ischemia of 20% in the aspirin arm, it was calculated that 260 patients would be needed to give sufficient power (85%) to show a 70% reduction in transient myocardial ischemia with heparin and aspirin compared with aspirin alone at the $p < 0.05$ level. Thus, 285 patients were entered on the assumption that ~10% of the patients included would, in retrospect, be diagnosed as having myocardial infarction, not unstable angina on admission. The chi-square test was used to compare categoric data, and the Student *t* test was used for continuous data. The developments of myocardial infarction and death were analyzed using the Kaplan-Meier method and the log rank test on the intention-to-treat principle. A subgroup analysis was also performed after excluding those patients shown retrospectively to have sustained a myocardial infarction at the time of admission.

Results

The two groups were similar with regard to gender, risk factors for coronary artery disease, previous angina and myocardial infarction and treatment history (Table 1). Patients in Group A were older (mean [±SEM] age 60.6 ± 0.8 vs. 58.3 ± 0.8 years, respectively, p = 0.04). There were ST-T wave changes on the admission ECG in more than two-thirds of patients (66.2% in Group H + A vs. 72.5% in Group A, p = NS). During the acute phase, similar numbers of patients in both groups received oral beta-blockers (76.0% in Group H + A vs. 74.0% in Group A, p = NS) and diltiazem (77.9% in Group H + A vs. 77.9% in Group A, p = NS). In the remaining patients, these drugs were either not begun or were withdrawn because of hypotension or bradycardia. Fifteen patients (six in Group H + A, nine in Group A) did not receive or could not tolerate aspirin because of dyspepsia, gastric erosions, peptic ulceration or aspirin allergy. Heparin therapy was started promptly after admission (mean 4.6 ± 1.2 h) and continued for 46.1 ± 1.1 h. The activated partial thromboplastin time on admission was 42 ± 1 s and increased to 101 ± 4 s with heparin administration. One patient in Group H + A had a hematemesis after 20 h of heparin therapy (activated partial thromboplastin time 69 s) that required blood transfusion. One patient in Group A developed a rectus sheath hematoma that required surgical evacuation under general anesthetic. The mean duration of hospital stay was 7.7 days for both treatment groups.

Table 1. Patient Characteristics of the Treatment Groups

	Group H + A (n = 154)	Group A (n = 131)
Female (%)	19.5	19.9
Mean (±SEM) age (yr)	58.3 ± 0.8*	60.6 ± 0.8
Current smoker	51 (33%)	31 (24%)
Former smoker	77 (50%)	67 (51%)
History of hypertension	48 (31%)	48 (37%)
Diabetes mellitus	13 (8%)	6 (5%)
Family history of IHD	88 (57%)	73 (56%)
Previous angina	81 (53%)	74 (57%)
Mean (±SEM) duration (mo)	46 ± 7	48 ± 8
Previous MI	62 (40%)	51 (39%)
Medication on admission		
Beta-blocker	52 (34%)	48 (37%)
Calcium antagonist	44 (29%)	41 (31%)
Nitrate (po/td)	51 (33%)	47 (36%)
Nitrate (sl)	37 (24%)	33 (25%)
Aspirin	52 (34%)	48 (37%)
Diuretic	26 (17%)	25 (19%)
ACE inhibitor	8 (5%)	10 (8%)
Cardiac enzymes >2 × ULN on admission	10 (7%)	15 (11%)

*p = 0.04 versus Group A. Data presented are mean values ± SEM or number (%) of patients. Group A = aspirin alone; Group H + A = combined heparin and aspirin therapy; IHD = ischemic heart disease; MI = myocardial infarction; po = oral; sl = sublingual; td = transdermal; ULN = upper limit of normal.

Transient myocardial ischemia. A total of 11,622 h of ST segment monitoring was obtained (Table 2). No data were available in four patients (one in Group H + A, three in Group A) because of technical problems. There were one or more episodes of transient myocardial ischemia in 18% of Group H + A and 24% of Group A patients (p = 0.18), giving a total of 244 episodes (96 in Group H + A vs. 148 in Group A, p = 0.17). There was no significant difference in total duration of ischemia in the two groups (2,911 min in Group H + A vs. 4,908 min in Group A, p = 0.21). One patient in Group A contributed a total of 1,360 min of transient ischemia, in which one episode lasted 1,062 min. Considering those patients with episodes of transient myocardial ischemia, 14 (52%, Group H + A) and 18 (58%, Group A) patients had a total of ≥60 min of ischemia (p = 0.83, Group H + A vs. Group A). The proportion of episodes with ST segment elevation was similar in both groups, as was the proportion of silent and painful episodes.

Analysis of the two treatment groups after exclusion of patients with a significant increase in cardiac enzyme levels on admission (Group H + A, 10 patients; Group A, 15 patients) with regard to the number of episodes, duration of transient myocardial ischemia and total ischemia revealed no significant differences between the two groups.

Adverse events. *Myocardial infarction and death.* Event-free survival from myocardial infarction or death was similar in both treatment groups (Fig. 1) and was unaffected

Table 2. Transient Myocardial Ischemia in the Patient Groups

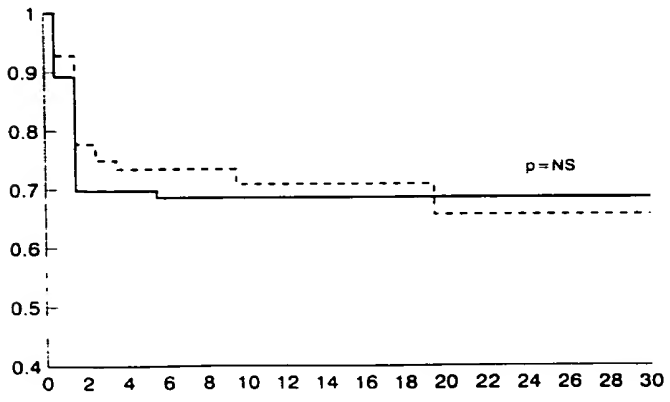
Tape Variables	All Patients	Group H + A	Group A
Total duration of ST segment monitoring (h)	11,622	6,114	5,508
Duration/pt (h)	40.9 ± 0.7	39.7 ± 1.0	42.2 ± 0.9
No. of pts (%) with ≥1 episode of TMI	58 (20%)	27 (18%)	31 (24%)
Total no. of episodes	244	96	148
Median/pt	0	0	0
Range/pt	0–23	0–12	0–23
Median episode duration (min)	15.0	13.5	16.0
Range (min)	1–1,062	1–467	1–1,062
Total duration of ischemia (min)	7,819	2,911	4,908
Episodes of ST segment elevation	72 (30%)	29 (30%)	43 (29%)
Silent episodes	190 (82%)	76 (79%)	114 (83%)
Pts with >60 min TMI	32/58 (55%)	14/27 (52%)	18/31 (58%)

Data presented are mean values ± SEM or number (%) of patients (pt, pts, Pts). TMI = transient myocardial ischemia; other abbreviations as in Table 1.

by the mode of presentation. The incidence of myocardial infarction or death (Table 3) was 53% in patients with a positive tape compared with 22% in patients with a negative tape ($p < 0.0001$). Five of the six deaths occurred in patients with transient myocardial ischemia. Although event-free survival from myocardial infarction or death was significantly lower in patients with episodes of transient myocardial ischemia compared with patients without (Fig. 2), there was no difference between the two treatment groups in this respect (Fig. 3). Among patients with episodes of transient myocardial ischemia, events were no more frequent in patients with ≥60 min of total ischemia compared with patients with <60 min of total ischemia.

Cardiac catheterization and revascularization. Similar numbers of patients in the two treatment groups underwent cardiac catheterization (31 [20%] in Group H + A, 23 [15%] in Group A) or revascularization by either angioplasty or coronary artery bypass surgery (19 [12%] in Group H + A, 15 [12%] in Group A). A total of 54 patients (19%) were transferred to a regional cardiothoracic center for cardiac catheterization (Table 3). There were more referrals overall among patients with than without episodes of transient myocardial ischemia (29% vs. 16%, respectively, $p = 0.04$), but there was no difference within the individual treatment groups in this respect. In Group H + A, 8 patients with transient myocardial ischaemia (30%) underwent cardiac catheterization, compared with 23 patients without transient ischemia (18%, $p = 0.18$). In Group A, 9 patients with transient myocardial ischemia (29%) underwent cardiac catheterization compared with 14 patients without transient ischemia (14%, $p = 0.06$). In the entire cohort of 285 patients, 34 underwent revascularization (17% of patients with transient myocardial ischemia, 11% of patients without) by either percutaneous coronary angioplasty or coronary artery bypass surgery during their hospital admission.

Figure 1. Event-free survival from myocardial infarction or death according to treatment. **Solid line** = aspirin alone; **dashed line** = combined heparin and aspirin therapy.



Effect of preadmission therapy. The incidence of myocardial infarction (fatal and nonfatal) was assessed in the entire study group according to preadmission therapy with beta-blockers, calcium antagonists and aspirin. The incidence of myocardial infarction was unaffected by preadmission therapy with beta-blockers or calcium antagonists but was lower in patients admitted taking aspirin compared with patients not previously taking aspirin (19% vs. 34%, respectively, $p = 0.01$).

Patients with a normal admission ECG. Episodes of transient myocardial ischemia occurred in only 2 patients (3.1%) with a normal ECG on admission, compared with 56 patients (22.7%) with abnormalities on the admission ECG ($p < 0.0001$). Events were infrequent in patients with a normal admission ECG (eight myocardial infarctions, four revascularization procedures, no deaths). In contrast, there were 73 myocardial infarctions ($p = 0.0001$ vs. patients with a normal admission ECG) and 30 revascularization procedures in patients with an abnormal ECG on admission; all the deaths

Table 3. Frequency of In-Patient Events According to Treatment and Presence or Absence of Transient Myocardial Ischemia

Event	TMI	All patients (n = 285)	Group H + A (n = 154)	Group A (n = 131)
MI or death (n = 82)	+	31/58 (53%)	16/27 (59%)	15/31 (48%)
	−	51/227 (22%)*	26/127 (20%)†	25/100 (25%)‡
Cardiac catheterization (n = 54)	+	17/58 (29%)	8/27 (30%)	9/31 (29%)
	−	37/227 (16%)§	23/127 (18%)	14/100 (14%)
PTCA/CABG (n = 34)	+	10/58 (17%)	6/27 (22%)	4/31 (13%)
	−	24/227 (11%)	13/127 (10%)	11/100 (11%)

*$p < 0.0001$ versus all patients with transient myocardial ischemia (TMI). †$p < 0.0001$ versus Group H + A patients with transient myocardial ischemia. ‡$p = 0.01$ versus Group A patients with transient myocardial ischemia. §$p = 0.04$ versus all patients with transient myocardial ischemia. Data presented are number (%) of patients. CABG = coronary artery bypass graft surgery; PTCA = percutaneous transluminal coronary angioplasty; + (−) = presence (absence) of transient myocardial ischemia; other abbreviations as in Table 1.

Discussion

The results of this study indicate that combination therapy with heparin and aspirin compared with aspirin alone confers no advantage with regard to both the presence of transient myocardial ischemia and in-hospital prognosis in patients with a clinical diagnosis of unstable angina. Unstable angina is a common cardiac condition that carries with it a significant risk of myocardial infarction and death. In the majority of cases the development of symptoms can be attributed to the fissuring or rupture of an atherosclerotic plaque in a coronary artery (1). Plaque disruption triggers a sequence of events that results in local thrombus formation and platelet activation (2,3). Consequently, myocardial blood supply is jeopardized, and ischemia may result. Complete occlusion of the coronary artery is associated with the development of myocardial infarction and the possibility of sudden cardiac death.

Recognition of the underlying pathophysiology has led to the development of various treatment strategies aimed at reducing the incidence of myocardial infarction and death in patients with unstable angina. Currently there are many drugs with theoretic potential, including agents with antiplatelet, antithrombotic and fibrinolytic properties. However, aspirin is the only drug that has been shown unequivocally to have a dramatic impact in altering the natural history of unstable angina (4–7). Four randomized placebo-controlled, double-blind trials of aspirin, using doses varying

Figure 2. Event-free survival from myocardial infarction or death according to the presence (**dashed line**) or absence (**solid line**) of transient myocardial ischemia.

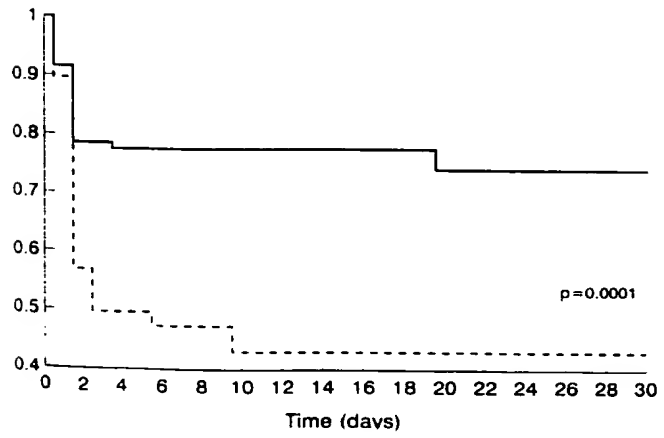
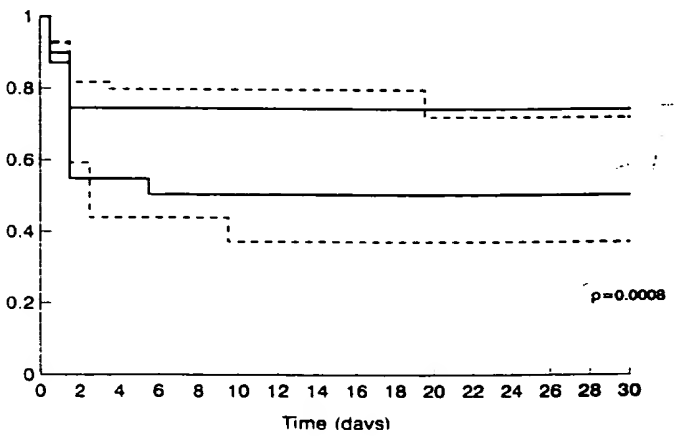


Figure 3. Event-free survival from myocardial infarction or death according to treatment and the presence or absence of transient myocardial ischemia. **Solid lines** = aspirin alone; **dashed lines** = combined heparin and aspirin therapy; **top lines** = absence of transient myocardial ischemia; **bottom lines** = presence of transient myocardial ischemia.



JACC Vol. 24, No. 1
July 1994:39–45

from 75 mg once daily (7) to 325 mg four times a day (5), have demonstrated a reduction in risk of nonfatal myocardial infarction and death >50%.

Earlier trials of heparin therapy. In contrast to the aspirin studies, the results that have emerged from trials of heparin therapy have been less concordant. The first randomized placebo-controlled study of heparin therapy in unstable angina reported a significant reduction in the incidence of myocardial infarction with heparin administration (8). The second placebo-controlled trial of heparin therapy compared aspirin versus heparin versus aspirin and heparin (6). The incidence of fatal or nonfatal myocardial infarction was reduced significantly in all three treatment arms compared with placebo therapy. More recently, the Research Group on Instability in Coronary Artery Disease (RISC) group (7) compared aspirin versus heparin versus aspirin and heparin in unstable coronary artery disease. In contrast to the previous study (6), the incidence of myocardial infarction and death in the heparin group was the same as in the placebo group. However, treatment with aspirin was effective, whether given as monotherapy or in combination with heparin. Possible reasons for the apparent lack of effect of heparin include a delay in the initiation of heparin therapy (median delay 33 h) and the use of intermittent intravenous heparin rather than a continuous infusion. In view of the uncertainty with regard to the effect of *intermittent* heparin therapy (7), we chose to give heparin as a continuous infusion.

Because aspirin is an established treatment in unstable angina, the most pertinent clinical question to be answered is whether combination therapy is better than treatment with aspirin alone. We were unable to demonstrate any superiority with combination therapy compared with aspirin alone. In the RISC study combination therapy was the only treatment superior to placebo therapy at 5 days ($p = 0.03$), although it was not significantly different from aspirin treatment alone. Beyond 5 days the aspirin and combined treatment arms merged. No significant differences between the three treatment arms with respect to fatal or nonfatal myocardial infarction were demonstrated by Theroux et al. (6). Taken together, these results suggest that there is no advantage from combination therapy compared with aspirin alone.

Effects of heparin and aspirin on transient myocardial ischemia. Transient myocardial ischemia is associated with an increased event rate in patients with unstable angina (9–11). We believe that our study is the first reported comparison of the effects of combined therapy versus aspirin on transient myocardial ischemia. Other investigators have examined the effects of treatment on the incidence of refractory angina (6), which is a more subjective end point and is not interchangeable with transient ischemia. Indeed, the vast majority of episodes of transient ischemia are silent (9,10) and are therefore unlikely to be detected clinically without the benefit of continuous ECG monitoring.

One earlier study compared the effects of monotherapy with heparin, aspirin and alteplase on transient myocardial ischemia in patients with refractory unstable angina (14). Heparin given as a continuous infusion, rather than intermittently, was the most effective treatment. Despite the known benefits of aspirin in unstable angina, the number and duration of ischemic episodes were not altered by aspirin therapy. We were unable to discern any advantage from combination therapy over aspirin alone with regard to either the incidence of transient myocardial ischemia, number of episodes or total duration of myocardial ischemia. Furthermore, the proportion of silent episodes and episodes with ST segment elevation was similar in the two treatment groups. One possible reason for the differing effect of the heparin-containing arm in our study and that of Serneri et al. (14) may relate to the groups studied. They studied a highly selected subgroup of patients that comprised only 24% of the original cohort. In contrast, we studied patients with a clinical diagnosis of unstable angina without ECG features of acute myocardial infarction. Consequently, we believe that our results bear more clinical relevance to the situation typically encountered in emergency departments and coronary care units.

Study limitations. *Unstable angina* is an umbrella term for several different pathophysiologic conditions associated with a new or altered pattern of angina. The risk of progression to myocardial infarction depends to an extent on clinical presentation (15). We defined unstable angina on the basis of history of the chest pain and absence of evolving Q wave myocardial infarction on the admission ECG. Thus, we have addressed the role of heparin and aspirin in the management of patients with presumed cardiac chest pain who traditionally would not receive thrombolysis in the absence of evolving myocardial infarction.

The incidence of myocardial infarction was higher in our study compared with other reports (4–7,16). The myocardial infarction rate will depend to an extent on the definition of unstable angina because non-Q wave myocardial infarction is sometimes included in the definition. Over 50% of the myocardial infarcts in our study were not associated with the development of pathologic Q waves, which probably accounts for the higher infarction rate in our study. Additionally, 25 patients had a significant increase in cardiac enzyme levels on admission but were recruited on an intention-to-treat basis. We elected not to use the results of cardiac enzymes as a criterion for inclusion or exclusion because these results were not available at the time of admission to hospital. Instead, we decided a priori to perform a subgroup analysis after exclusion of such patients.

The results of our study should not be extrapolated to the use of heparin as monotherapy in unstable angina. Although we did not assess heparin therapy in isolation, there is evidence that continuous intravenous heparin is as effective as aspirin in preventing myocardial infarction (6). Therefore, patients in whom aspirin is contraindicated may be candidates for heparin therapy. However, a rebound phenomenon has been observed shortly after discontinuation of heparin that appears to be prevented by the coadministration of aspirin (17).

Conclusions. The results from this study indicate that the combination of heparin, administered as a continuous intravenous infusion, and aspirin confers no benefit to the patient, compared with treatment with aspirin alone, with regard to either in-hospital prognosis or frequency and duration of transient myocardial ischemia. The presence of transient ischemia on 48-h monitoring is associated with a poor prognosis. Because the vast majority of episodes of transient ischemia are silent, consideration should be given to more widespread use of ST segment monitoring in the acute phase of unstable angina.

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